Progression of atherosclerosis in arteries distal to lower extremity revascularizations

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Purpose: **The characteristics of progression of atherosclerotic occlusive disease (AOD) of the lower extremities after revascularization are unknown. Duplex scanning or angiography were used to determine progression in 150 patients after they underwent revascularization for AOD.**

Methods: **Follow-up studies were compared with presurgical arteriograms. Superficial femoral (SFA) and popliteal arteries were graded as less than 50% stenosis, 50% to 99% stenosis, or occluded. Tibial arteries were graded with regard to whether they were continuously patent from the popliteal trifurcation to the ankle. Progression was defined as an increase in one stenosis category.**

Results: **At a mean follow-up of 4.8 years, 18% of native arteries, 39% of extremities, and 52% of patients demonstrated progression of AOD. Overall, 21% of arteries in patients undergoing infrainguinal bypass and 14% of arteries in patients undergoing suprainguinal bypass demonstrated progression ($p = 0.004$). Progression was more frequently detected in examinations performed more than 4 years after baseline arteriography (66%) than in examinations performed 6 months to 2 years (45%, $p = 0.032$) or 2 to 4 years (44%, $p = 0.029$) after baseline arteriography. Thirty percent of SFAs demonstrated progression, and 32% with 50% stenosis or greater at baseline became occluded. There was no difference in SFA, popliteal, or tibial artery progression in revascularized versus nonrevascularized extremities after suprainguinal bypass. There was no difference in tibial artery progression in operated and nonoperated limbs after femoropopliteal artery bypass.**

Conclusions: **AOD progression occurs frequently in patients requiring revascularization and is more prevalent in patients requiring femoropopliteal than in patients requiring suprainguinal bypass. AOD progression in patients undergoing vascular surgery is associated with the pattern of disease producing lower extremity ischemia and does not appear to be worsened by arterial reconstruction. (J VASC SURG 1995;22:450-6.)**

Each year many thousands of major lower extremity revascularizations are performed to treat symptoms of lower extremity atherosclerosis.[1-3] Despite the major morbidity potentially associated with progression of lower extremity atherosclerotic occlusive disease, anatomic progression of atherosclerosis has only been studied directly in coronary, cervical, carotid, and renal arteries.[4-7] Studies of lower extremity atherosclerosis progression have almost exclusively been indirect, on the basis of either symptoms, segmental Doppler pressures, or the need for amputation.[8-10] Surprisingly even postoperative patients who potentially have the most to lose from progression of lower extremity atherosclerosis have not been systematically studied for progression of arterial disease. Postoperative studies in patients undergoing revascularization have instead focused almost exclusively on graft patency.[11,12] Information regarding progression is needed to properly design studies of medical and surgical therapies of lower extremity atherosclerosis, as well as to determine whether revascularization adversely influences progression of arterial disease.

Direct studies of progression of lower extremity atherosclerosis have been limited because of the need for angiography to accurately evaluate lower extremity arteries. However, duplex scanning of lower extremity arteries has now achieved sufficient accuracy that it can be used to evaluate the lower extremity

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arterial circulation from the aortic bifurcation to the ankle.[13] In this study, we used duplex scanning or follow-up arteriography to detect progression of lower extremity atherosclerosis in operated and nonoperated limbs of patients at varying intervals after arterial reconstruction for chronic lower extremity ischemia.

The study was designed to address the following clinical questions. First, what is the prevalence of progression of atherosclerosis in arteries distal to lower extremity revascularization? Second, is progression more frequent in extremities undergoing aortoiliac revascularization than in those undergoing femoropopliteal revascularization? Third, is progression more frequent in operated or unoperated extremities?

METHODS

Patient selection and grouping of lower extremities. Consecutive patents in the vascular surgery outpatient clinic were recruited from those who had an inflow procedure (aortofemoral, crossfemoral, or axillofemoral bypass or an iliac artery balloon angioplasty) or a femoral popliteal bypass for occlusive atherosclerotic disease. Patients were eligible for study if at least 6 months had passed since revascularization was performed. Each patient was characterized with respect to atherosclerotic risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, chronic renal insufficiency (serum creatinine greater than 1.5 mg/dl on two separate determinations), and whether they smoked at any time during follow-up. The study was approved by the Institutional Review Boards of both the Oregon Health Sciences University and the Portland, Oregon Department of Veteran's Affairs Hospital. All patients signed informed consent.

Each leg was classified into one of four groups. Nonoperated lower extremities were classified into group 1, those contralateral to an extremity with a femoropopliteal bypass, or group 2, those acting as the donor artery in a femorofemoral bypass or those contralateral to an iliac artery balloon angioplasty. Extremities with an arterial reconstruction were classified as having had an inflow procedure (aortobifemoral or axillobifemoral bypass or iliac artery balloon angioplasty) (group 3) or a femoropopliteal bypass (group 4).

Baseline lower extremity arteriography. The status of the arteries on the patient's initial preoperative arteriogram was used as the basis for evaluating subsequent progression of arterial occlusive disease. In groups 1, 2, and 3, superficial femoral and popliteal arteries were evaluated. Superficial femoral and popliteal arteries were not evaluated in follow-up in extremities initially undergoing a femoropopliteal bypass (group 4). This is because in group 4 extremities, the superficial femoral artery was generally occluded at baseline, and progression of disease in the popliteal artery caused by paraanastomotic fibrointimal hyperplasia rather than atherosclerosis cannot be distinguished by duplex scanning. In all groups, anterior and posterior tibial arteries were classified with regard to whether they were continuously patent from the level of the popliteal trifurcation to the ankle. Tibial arteries that were initially segmentally occluded were classified as occluded. The peroneal artery was not studied because previous studies have shown that it is less accurately assessed with duplex scanning than the anterior and posterior tibial arteries.[13]

Follow-up studies. Follow-up examination was performed with angiography (20% of examinations) or duplex scanning (80% of examinations). Duplex scanning represented the only procedure obtained solely for the purposes of the study. Arteriography was obtained if clinically indicated. Both accuracy and technique of lower extremity arterial duplex scanning in our laboratory have been previously reported.[13]

Some patients had more than one follow-up examination. This occurred when patients had intervening arteriograms before the final examination obtained for the study or when patients had secondary operative procedures.

Superficial femoral and popliteal arteries were graded on follow-up angiography or duplex examination as either 0% to 49%, 50% to 99%, or occluded. Each anterior and posterior tibial artery continuously patent on the initial preoperative arteriogram was graded on follow-up examination with regard to whether continuous patency was maintained from the popliteal trifurcation to the ankle. Disease progression was defined in the femoral and popliteal arteries as an increase in one category of stenosis. Progression was defined for the anterior and posterior tibial arteries as a vessel continuously patent from the popliteal trifurcation to the ankle subsequently becoming either segmentally or totally occluded.

Data analysis. Follow-up examinations were grouped with regard to whether they occurred 6 months to 2 years, 2 to 4 years, or more than 4 years after the baseline arteriogram was obtained. Prevalence of arterial occlusive disease progression in each extremity group was determined by analysis for any

progression detected by duplex scanning or angiography compared with baseline arteriography. Prevalence of disease progression in operated and unoperated extremities in patients after undergoing a suprainguinal procedure (groups 2 and 3) was compared with operated and unoperated extremities in patients undergoing an infrainguinal procedure (groups 1 and 4). The influence of suprainguinal revascularization on progression of distal occlusive disease was determined by comparing disease progression in the superficial femoral, popliteal, and tibial arteries in unoperated limbs (group 2) and operated limbs (group 3). Tibial artery progression in unoperated limbs (group 1) was compared with operated limbs (group 4) to determine the influence of infrainguinal reconstruction on distal disease progression.

Statistical analysis. Statistical methods included *t* test and chi-squared analysis. Multivariate stepwise logistic regression analysis was used to control for the potential confounding effect of risk factors on atherosclerotic progression. In all analyses, groups were considered significantly different if $p < 0.05$.

RESULTS

Patients. One hundred fifty patients were entered into the study; 104 were men, and 46 were women. The mean age was 66.5 years (range 34 years to 93 years). Sixty-four percent had hypertension, 25% had diabetes, 33% had hypercholesterolemia, 14% had chronic kidney failure, and 89% continued to smoke during the follow-up period.

Two hundred six follow-up examinations were performed in the 150 patients. One hundred three patients underwent a single examination, 38 patients underwent two examinations, and 9 patients underwent three examinations. Ninety-four examined extremities were not revascularized. Fifty-one were contralateral extremities in patients with a femoropopliteal bypass graft (group 1) and 43 were either the donor extremities for femoral-femoral bypass grafts or were contralateral to iliac artery angioplasties (group 2). Ninety-three examined extremities had suprainguinal procedures (group 3), and 77 had femoropopliteal bypass grafts (group 4). A total of 264 extremities were therefore studied. The remaining 36 extremities were excluded because of inadequate baseline angiography or prior amputation.

Initial arteriogram. In the 264 eligible extremities, 83% (765/926) of the arteries were patent on the initial arteriogram and could be used as a basis for comparison with the follow-up arteriogram or duplex scan (Table I). There were 159 patent superficial femoral arteries, 171 patent popliteal arteries, 205 patent anterior tibial arteries, and 230 patent posterior tibial arteries.

Progression of arterial occlusive disease. Seventy-nine (53%) of the 150 patients had progression of arterial occlusive disease in at least one artery (mean follow-up 4.8 years, range 0.5 years to 20 years). Twenty-one percent of the arteries examined (67 of 324) and 66% of patients examined at greater than 4 years after baseline arteriography demonstrated detectable progression of disease. Fifteen percent of the arteries examined (47 of 313) and 44% of patients examined 2 to 4 years after baseline arteriography demonstrated disease progression. Seventeen percent of the arteries examined (47 of 351) and 45% of the patients examined 6 months to 2 years after baseline arteriography demonstrated disease progression. The likelihood of a patient demonstrating detectable disease progression was significantly greater at more than 4 years after baseline arteriography than at 2 to 4 years ($p = 0.029$) or at 6 months to 2 years ($p = 0.032$).

Overall, 18% of the 755 arteries patent on the baseline arteriogram had detectable disease progression on follow-up examination. Fifty-two of 159 (30%) patent superficial femoral arteries on baseline arteriography had progression of occlusive disease on follow-up study. Thirty-two percent of superficial femoral arteries with a 50% or greater stenosis ($n = 31$) at baseline arteriography progressed to occlusion. Two superficial femoral arteries were noted to have regression of atherosclerosis from 50% to 99% to less than 50%. Regression was documented by arteriography in one patient and by duplex scanning in the other. Fourteen percent of patent anterior and posterior tibial arteries at baseline arteriography ($n = 435$) were found on follow-up examination to have either total or segmental occlusion. No recanalization of previously occluded arteries was observed. There was no significantly increased prevalence of progression detected on follow-up when patients were stratified to age, sex, and atherosclerotic risk factors; $p > 0.05$ for all variables tested.

Arteries in patients undergoing infrainguinal bypass (groups 1 and 4) demonstrated significantly more progression than those in patients undergoing suprainguinal bypass (groups 2 and 3); 21% versus 14%, respectively ($p = 0.004$) (Table II). Multivariate stepwise logistic analysis also revealed a history of smoking ($p = 0.04$, odds ratio 3.8) and length of follow-up ($p = 0.02$) to be significant in contributing to progression in patients undergoing infrainguinal bypass. Adjusting for these factors did not

Table I. Patent arteries (n = 765) on initial arteriography in 150 patients undergoing operation for chronic lower extremity ischemia*

	Artery			
	Superficial femoral (no.)	*Popliteal (no.)*	*Anterior tibial (no.)*	*Posterior tibial (no.)*
Group 1	36	44	35	41
Group 2	37	37	31	33
Group 3	86	90	79	92
Group 4	NA	NA	60	64
Total	159	171	205	230

NA, Not applicable.
*Group 1, Nonoperated contralateral extremity in a patient with a femoropopliteal bypass; group 2, donor extremity in a patient with a femorofemoral bypass and extremities contralateral to an iliac artery balloon angioplasty; group 3, extremities revascularized with a suprainguinal bypass or angioplasty; group 4, extremities revascularized with a femoral popliteal bypass.

Table II. Number (percent) of arteries with detectable progression of arterial occlusive disease in examinations performed at 6 months to 2 years, 2 to 4 years, and greater than 4 years after lower extremity infrainguinal or suprainguinal revascularization

	Observation interval		
Groups	*6 months-2 years*	*2-4 years*	*>4 years*
Infrainguinal			
Group 1			
Superficial femoral	6/23 (26)	5/12 (41)	5/9 (56)
Popliteal	5/26 (19)	3/14 (21)	3/11 (27)
Tibial (Ant. and Post.)	9/40 (23)	4/24 (13)	2/23 (9)
Group 4			
Tibial (Ant. and Post.)	9/78 (12)	8/64 (13)	23/62 (37)
Totals	29/167 (17)	20/114 (18)	33/105 (31)
Suprainguinal			
Group II			
Superficial femoral	4/15 (27)	2/17 (12)	2/10 (20)
Popliteal	1/16 (6)	1/20 (5)	2/15 (13)
Tibial (Anterior and Posterior)	0/24 (0)	6/40 (15)	2/15 (13)
Group III			
Superficial femoral	7/35 (20)	6/40 (15)	16/50 (32)
Popliteal	2/16 (7)	2/40 (5)	4/41 (4)
Tibial (Anterior and Posterior)	4/62 (6)	22/80 (28)	8/88 (9)
Totals	18/182 (10)	39/237 (16)	34/219 (16)

*Groups
Group I: Non-operated contralateral extremity in a patient with a femoral popliteal bypass
Group II: Donor extremity in a patient with a femoral to femoral bypass; extremities contralateral to an iliac artery balloon angioplasty
Group III: Extremities revascularized with a suprainguinal bypass or angioplasty
Group IV: Extremities revascularized with a femoral popliteal bypass

change thc result that having a femoropopliteal bypass is in itself a risk factor for greater progression of arterial occlusive disease (p = 0.009, odds ratio 2.8). In patients examined more than 4 years after infrainguinal bypass (groups 1 and 4), progression was found in 31% of the arteries. Progression was found in 16% of the arteries in patients examined more than 4 years after a suprainguinal bypass (extremity groups 2 and 3) (p = 0.003) (Table II). Progression was particularly frequent among the initially nonoperated extremities of patients who had a femoral popliteal bypass. Forty percent of group 1 extremities examined more than 4 years after baseline arteriography demonstrated progression of femoropopliteal disease compared with 16% of group 2 (p = 0.163) and 22% of group 3 extremities (p = 0.140). This was due to progression of femoropopliteal disease in group 1 extremities because tibial artery progression occurred in only 9% of group 1 extremities versus 37% of Group 4 extremities examined at 4 years (p = 0.025) (Table II).

There were no significant differences in the prevalence of superficial femoral artery or popliteal artery progression in revascularized versus nonrevas-

cularized extremities of patients undergoing suprainguinal bypass. Similarly, except in examinations performed at more than 4 years (37% versus 9%, $p = 0.001$), there was no difference in tibial artery progression in operated and nonoperated extremities of patients undergoing femoropopliteal bypass (Table II).

DISCUSSION

Despite the prevalence of symptomatic lower extremity atherosclerosis, little is known with respect to its progression after lower extremity revascularization. To our knowledge, this study represents the first attempt to systematically gather anatomic data in a large number of patients documenting the prevalence of segmental progression of lower extremity atherosclerosis after revascularization for chronic lower extremity ischemia. This study was possible because of the documented accuracy of lower extremity arterial duplex scanning in assessing infrainguinal arteries from the groin to the ankle.[13]

This study demonstrates that progression of lower extremity atherosclerosis after revascularization occurs frequently. After a mean follow-up interval of 4.8 years, 53% of the 151 patients evaluated had progression of lower extremity atherosclerosis on follow-up angiographic or duplex examination. Not surprisingly, the prevalence of detectable disease progression increased significantly with increased length of follow-up. Only two patients exhibited spontaneous regression of superficial femoral artery stenosis from 50% to 99% to less than 50%. This reconfirms the observations of Brown et al.[14] that spontaneous regression of atherosclerotic arteries, although infrequent, can occur.

The 53% prevalence of disease progression demonstrated by anatomic studies in this group of patients who required lower extremity revascularization is higher than that documented by previous studies that use clinical history or indirect vascular laboratory testing of patients with intermittent claudication. Schadt et al.[15] determined that, in 362 patients with intermittent claudication and monitored for an average of 9 years, only 7% showed evidence of symptomatic worsening by clinical history. Jonason and Ringquiest[16] found in 224 patients with claudication that 21% of patients progressed by segmental cuff pressures over a mean follow-up of 6 years. The higher prevalence of progression in our study reflects the fact that considerable anatomic disease progression can occur without a change in clinical status.

These data, in contrast to previous studies with clinical endpoints to determine progression, indicate future studies seeking to document the effects of atherosclerotic risk factor modification and medical therapies on progression of lower extremity atherosclerosis will probably require fewer patients to determine efficacy if anatomic rather than clinical endpoints are used. This study may serve as a basis for power calculation to determine the minimum number of patients required for randomization to detect the efficacy of a particular treatment on lower extremity atherosclerotic disease progression at certain time intervals. For example, if a drug under investigation is proposed to significantly decrease atherosclerotic progression by 10% over 4 years in patients with chronic lower extremity ischemia, 1700 patients will be required for randomization if a prevalence of patient progression from our study of 66% at greater than 4 years is used. In contrast, a drug proposed to delay progression by 50% would require only 70 patients to be randomized if the same progression rate and time interval from our study are applied.

With the possible exception of smoking, none of the risk factors for atherosclerosis examined in this study were associated with higher prevalence of progression. This may indicate that patients with advanced lower extremity ischemia have well-established atherosclerosis that will inevitably progress in their lower extremities. As is true of most studies of lower extremity ischemia, the prevalence of risk factors was very high. For instance, only 16 of 151 patients were nonsmokers. Walsh et al.[17] also found that, in 38 patients evaluated by angiography or duplex scanning for progression of superficial femoral artery atherosclerosis, progression was not influenced by sex, age, diabetes, hypertension, or cessation of smoking.

There was no consistent difference in the prevalence of progression of lower extremity atherosclerosis in revascularized versus nonrevascularized limbs of patients undergoing revascularization for iliac artery occlusive disease or in the tibial arteries of operated and nonoperated limbs of patients undergoing femoral popliteal bypass. Overall, however, progression was more prevalent in the arteries of patients undergoing operation for infrainguinal rather than suprainguinal occlusive disease. This difference was primarily due to the high prevalence of progression of femoropopliteal disease in the contralateral limbs of patients initially undergoing femoropopliteal bypass. It therefore appears that revascularization in itself does not alter the progression of lower extremity atherosclerosis but that overall pro-

gression may be related to whether the patient's disease is primarily suprainguinal or infrainguinal. Patients admitted requiring an infrainguinal arterial reconstruction are clearly older and in part because of this may have more aggressive atherosclerosis and ultimately a poorer prognosis than younger patients admitted for suprainguinal revascularization. Certainly we and others have documented low overall survival rates in patients requiring infrainguinal arterial reconstruction.[18,19] Because most patients in this study were only examined at a single point after surgery, the differences noted between groups should be regarded as tentative. Prospective longitudinal studies will be required to document progression of atherosclerosis in patients with lower extremity arterial occlusive disease, as well as to establish conclusively any differences because of disease pattern and the type of revascularization.

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DISCUSSION

Dr. D. Eugene Strandness (Seattle, Wash.). This study by McLafferty and his colleagues at Oregon presents preliminary data on disease progression in lower limb atherosclerosis. As noted this study represents one glimpse in time at variable intervals after the disease was first detected. The methods used were arteriography at the first visit followed by duplex scanning at later times. The categories used were less than 50%, greater than 50%, and occlusion for the femoropopliteal segment and patency to occlusion for the arteries below the knee. Progression was inferred by moving from one duplex category to a higher one for the femoropopliteal and tibial artery segments.

The rate of progression was greater in patients undergoing infrainguinal bypass as compared to those with suprainguinal surgery—21% versus 14% ($p < 0.004$). As expected the likelihood of finding disease progression was higher with longer follow-up. Surprisingly they could find no differences in the rate of progression when the patients were stratified by risk factors such as diabetes.

This study raises several interesting questions about

disease progression, how it should be detected, and its impact on both limb function and outcome with or without surgery. The areas of great interest are as follows: (1) The distribution of disease is different in patients with type 2 diabetes and patients without diabetes. It is well known that suprainguinal disease is less frequent in patients with type 2 diabetes, the same in the femoropopopliteal area and higher in the tibial and peroneal arteries. We have shown that both the prevalence and progression rates for these two populations are different. In our studies, the patients were recruited for long-term follow-up and were not first seen in a vascular clinic. These are different populations as compared with this series. For example the prevalence in patients with type 2 diabetes was 22% compared with 3% in our control subjects. At 2 years 18% of the patients with type 2 diabetes had development of new disease, and 87% showed worsening by ankle/brachial indexes (ABI). (2) How can disease progression be documented? In our studies we used the ABI alone, which reflects global changes and does not assess the site or manner of disease progression. Obviously, it would be best to combine the pressure measurements with imaging. (3) Atherosclerosis progresses in two ways that are important but difficult to document unless one examines the arterial segment directly by some imaging technique as was used here. A plaque can progress by simply increasing the degree of narrowing or the involved arterial segment can thrombose leaving the artery totally occluded. It would be interesting to know which of these mechanisms were more common. Although there is little doubt that thrombosis is a very common terminal event, it is not yet clear if this is a process independent of the atherosclerosis itself. (4) For the patient and the physician, the importance of disease progression relates to limb function—the extent to which walking ability is decreased and ultimately the likelihood of limb loss. Limb loss rates are extremely low with this disease even when untreated, so I doubt if this question can be answered without very large numbers of patients. (5) For us as surgeons disease progression can be an important cause of graft failure, but it is my impression from our own studies that it is a relatively infrequent cause of vein graft loss. This would appear to be borne out by the numerous ongoing studies of vein graft function and how long-term patency can be increased.

Finally, from an epidemiologic standpoint, it will be important to assess the role of contributing risk factors on disease progression. This might permit us to assess which risk factors can be controlled and reduce the rate of progression. In our own studies we examined the impact of single risk factors and combinations to assess their impact on both the prevalence of disease and rate of progression. It became clear that risk factors appear to be additive.

Finally, there are only two areas in the arterial circulation where these types of studies can be done by examining the arteries directly. These are of course the carotid and peripheral arteries. The coronary arteries have been the most widely studied, but here one is forced to look at either death or myocardial infarction as the outcome variables.

Dr. Robert B. McLafferty. Your first question is an excellent one regarding the risk factors, and at first glance it may seem surprising that the risk factors didn't seem to vary with progression in this study. The important point regarding this study is that the risk factors didn't involve our original question in terms of determining prevalence of progression. We did screen the patients and determine what the risk factors were in this particular group with severe atherosclerotic disease, but the study was very biased toward a group of patients having many atherosclerotic risk factors. Those patients who did not have risk factors were few. Therefore we could not achieve statistical significance in the differences. This study does not contradict previous studies specifically examining the questions of smoking or diabetes.

With regard to your question of documenting progression, this study hasn't been correlated yet to patients' symptoms or ABIs. I think that's a very important question that needs to be answered.

In terms of addressing the question about whether occlusion leads to thrombosis or thrombosis occurs before critical stenosis, I don't believe our study regarding that question can be answered. It's a very interesting phenomenom to study. Perhaps a well-controlled animal model could answer that specific question.

With regard to vein graft failure caused by development of poor outflow, our study didn't show any differences in progression in arteries distal to revascularizations except at greater than 4 years for femoropopliteal bypasses. That may be one reason that outflow is not a major cause of graft flow failure.

Dr. Calvin B. Ernst (Detroit, Mich.). Did you correlate progression of outflow disease with the type of bypass used? Can the prosthetic graft flow surface be implicated in activation of mitogenic factors to cause progression of outflow disease? It might be worth looking at the prosthesis or bypass used and correlate this with progression of outflow disease.

Dr. McLafferty. Well, unfortunately, in this study all the patients with a femoropopliteal bypass had vein bypass, and we did not have any patients with polytetrafluoroethylene (PTFE). With regard to the donor extremity of our inflow or suprainguinal revascularizations, all patients had femorofemoral bypasses that used PTFE. I think that your point regarding platelet activation and whether there's some sort of relationship between that and PTFE is a good one. I'm not sure how we could address or study that particular part of your question regarding the data in this study.